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Total Synthesis of Bassiatin and Its Stereoisomers: Novel Divergent Behavior of Substrates in Mitsunobu Cyclizations

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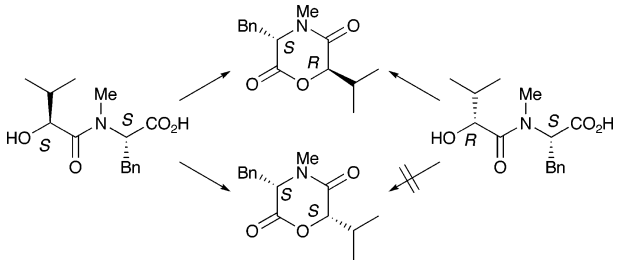

Total syntheses of the morpholine-2,5-dione, Bassiatin, and its stereoisomers have been completed. A key step in the syntheses was the Mitsunobu cyclization of hydroxyacid acyclic precursors. The hydroxyacid precursors are hindered alcohols and two substrates underwent Mitsunobu cyclization with retention of configuration. The other two substrates underwent Mitsunobu cyclization with either retention or inversion of configuration depending on reaction conditions. This divergence in outcome of the Mitsunobu reaction for the same substrate depending on effective concentration is novel.

Introduction

We are interested in the synthesis of bioactive modified peptides specifically those that are *N*-methylated as *N*-methylation confers changes on the peptide, such as increased membrane permeability,[1,2] proteolytic resistance,[1,3,4] and conformational rigidity[1,5] that may be therapeutically useful. Accordingly, our recent papers have focused on the synthesis of *N*-methyl amino acid monomers in suitable form for application in either solution or solid-phase synthetic protocols.[6−8] We now wish to report the results of our first foray into the synthesis of a natural product incorporating *N*-methyl amino acid monomers. The research has revealed a novel concentration effect influencing the stereocontrol in Mitsunobu cyclizations of hindered substrates.

Our target, Bassiatin **1**, is a morpholine-2,5-dione or depsipeptide that has shown anticoagulant activity. This compound was isolated and synthesized by Kagamizono et al.[9] The authors adopted two approaches to the morpholine-2,5-diones and the synthetic sequences are summarized in Scheme 1. One approach could be described as a lactonization approach and the other as a lactamization approach. Both sequences were successful in preparing the target compounds but they suffered from low yields at key steps.

A retrosynthetic analysis of Bassiatin is shown in Figure 1. In planning the synthesis of Bassiatin and its stereoisomers an orthogonal protection strategy was preferred as it was known the dimer-like precursors, like structure **2**, might be trimerized and then cyclized to afford a range of compounds exemplified by the natural product Enniatin **3**.[10] Bassiatin **1** was disconnected to give the *N*-methyl amide **2**. This in turn could be cleaved

(1) Fairlie, D. P.; Abbenante, G.; March, D. R. *Curr. Med. Chem.* **1995**, *2*, 654.
(2) Cody, W. L.; He, J. X.; Reily, M. D.; Haleen, S. J.; Walker, D. M.; Reyner, E. L.; Stewart, B. H.; Doherty, A. M. *J. Med. Chem.* **1997**, *40*, 2228.
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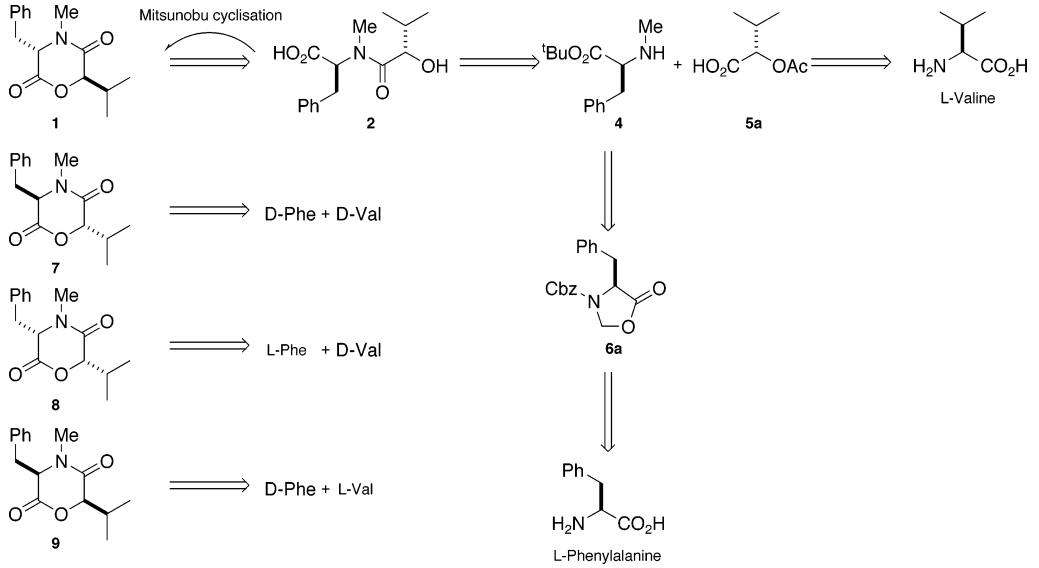
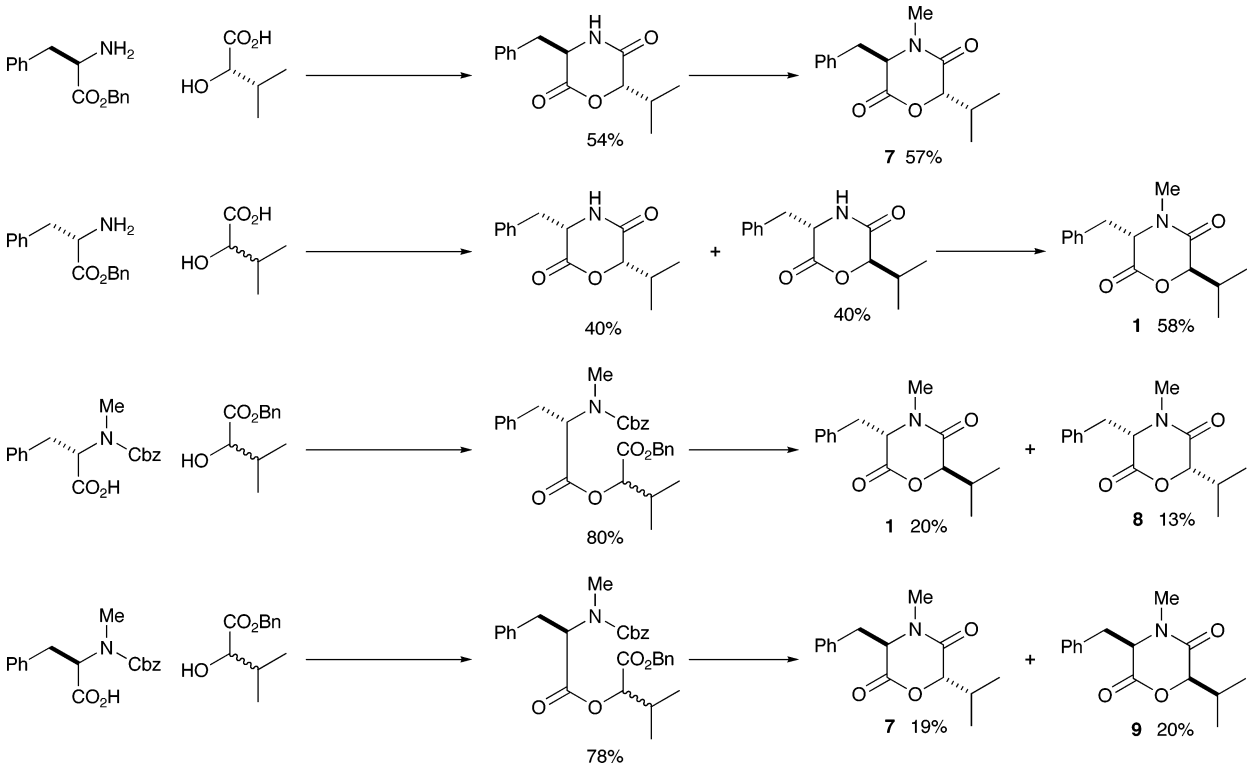


FIGURE 1. Retrosynthetic analysis of Bassiatin **1** and its stereoisomers **7**–**9**.

SCHEME 1



to the *N*-methyl phenylalanine **4** and the α-acetoxy acid **5a**. L-Phenylalanine can be converted through the 5-oxazolidinone **6** into the *N*-methyl monomer **4**.[11] L-Valine participates in a diazotization reaction with retention of configuration to give the acetate **5a**.[12,13]

Coupling of compounds **4** and **5a** and deprotection of the acid and alcohol functionalities would give the amide **2**. This approach removes the need for a late-stage *N*-methylation of the amide, which Kagamizono et al.[9] found was low yielding. To expand the methodology for synthesis of the natural product and its stereoisomers it was proposed to complete the sequence by cyclizing the hydroxy acid **2** by using the Mitsunobu reaction.[14] Thus the (*S*)-alcohol **2** would give Bassiatin **1**, (*R*)-configured at C-6 of the morpholine-2,5-dione. In a similar vein, compounds **7**, **8**, and **9** would be prepared from combinations of D- and L-phenylalanine and D- and L-valine. Last, the isomers, like structures **10** and **11**, were of some interest.

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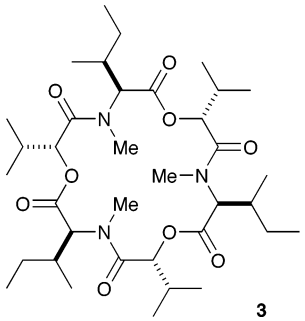

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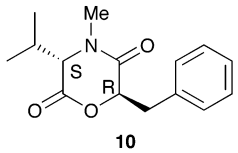

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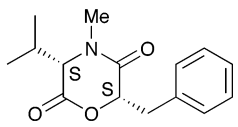

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Results and Discussion

The *N*-methyl amino acid precursors **6a**,[6] **6b**,[6] and **6c**[6] were made according to the sequence in Scheme 2. The oxazolidinone **6a** was reductively cleaved to give the *N*-methyl amino acid **12a**.[6] The carboxylic acid was then protected as the *tert*-butyl ester **13a** (90%). Similarly, the *tert*-butyl esters **13b** and **13c** were isolated in 90% and 90% yields, respectively. Hydrogenolysis then gave the required *N*-methyl amino acid **4a**, which was not purified further and was ready for coupling to the α-hydroxy acid partner. The enantiomeric ester **4b** was prepared by an identical sequence of reactions starting from oxazolidinone **6b**. Similarly, the *N*-methyl valine *tert*-butyl ester **4c** was prepared from the oxazolidinone **6c** via intermediates **12c** and **13c**.

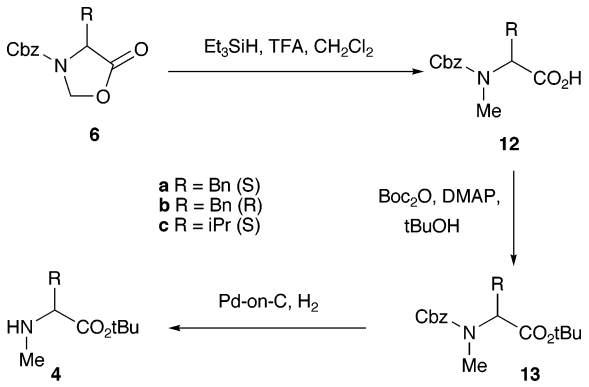
Kolasa and Miller[12] have reported the conversion of α-amino acids to the corresponding α-acetoxy acids by treatment with sodium nitrite and acetic acid. This diazotization proceeds with retention of configuration. Accordingly, L-valine **14a** and D-valine **14b** and L-phenylalanine **14c** and D-phenylalanine **14d** were diazotized and gave the expected acetates **5a**, **5b**, **5c**, and **5d** in 73%, 75%, 70%, and 71% yields, respectively, ready for coupling to the *N*-methyl amino acid partners.

The coupling reactions of the acids **5a** and **5b** and the amines **4a** and **4b** to form amides **15**−**17** were attempted initially with bromotripyrrolidinophosphonium hexafluorophosphate (PyBrop) as the coupling agent (Scheme 4). Table 1 shows the yields of these reactions were low. An increase in the chemical yield of about 30−35% was observed when the coupling agent was changed to *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU). The yields with HATU were routinely 65−75%.

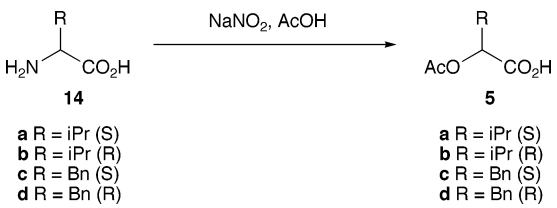
The amide **18** was formed from the coupling of compounds **4c** and **5d** and it was then converted to the hydroxy acid **19**. However, coupling of compounds **4c** and **5c** did not give the expected outcome. Instead of forming the amide **20**, a mixture of compounds **18** and **20** was isolated, in which compound **18** was the major component. Evidently, the activated acid intermediate in the amide coupling reaction or the desired product **20** is prone to epimerization of the α-center. This result had consequences for subsequent Mitsunobu studies discussed later.

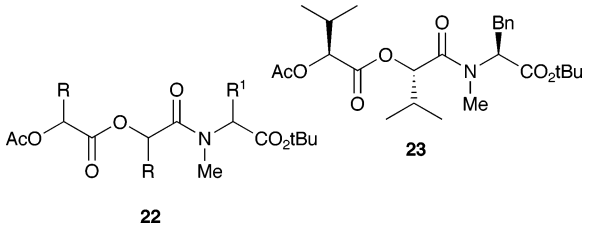
However, even with these improved coupling yields there was some evidence the acetate was being cleaved, presumably from the target amides **15**−**18** and **21**, under the reaction conditions. This cleavage allowed an extra reaction to occur resulting in the formation of trimeric compounds **22**. The formation of these trimers, in reactions to form amides **15**−**17** and **21**, was evident from TLC analysis of the reaction mixtures and it was confirmed by the presence of a peak at *m*/*z* 478 (M + H) in the electrospray mass spectrum corresponding to the general structure **23**. Alternative protecting groups such as *tert*-butyl and benzyl ethers were considered to overcome the acetate loss, but installation of these groups added extra synthetic steps to the sequence and they were not pursued. These trimeric side products were present in small amounts, which could be further reduced by ensuring the reaction mixture was maintained at 0 °C and the reaction time was 2 h.

SCHEME 2



SCHEME 3





22 **23**

Removal of the *tert*-butyl and acetate esters was attempted with aqueous lithium hydroxide in methanol. However, some epimerization of the substrate was observed and this was attributed to the sensitivity of *N*-methyl amino acids to base.[15] Treatment of the amides **15**−**18** and **21** with 2 N hydrochloric acid/dioxane effected removal of the *tert*-butyl and acetate esters without racemization to afford the hydroxyacids **19** and **24**−**27** in 51−54% yield.[8]

Mitsunobu Cyclizations. The hydroxyacids **24** and **26** were added to premixed solutions of triphenylphosphine and diethylazodicarboxylate (DEAD) in tetrahydrofuran in an attempt to prepare the *S*,*S*- and *R*,*R*-configured morpholine-2,5-diones **8** and **9**, respectively. The reaction products were difficult to purify due to the persistence of triphenylphosphine oxide and the DEAD

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SCHEME 4

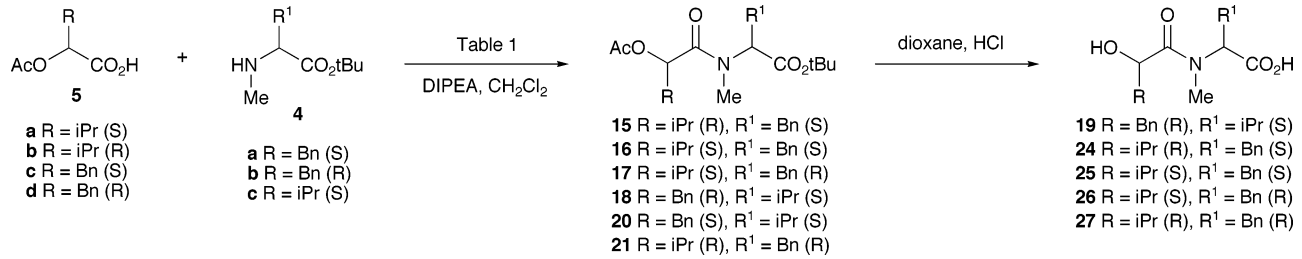
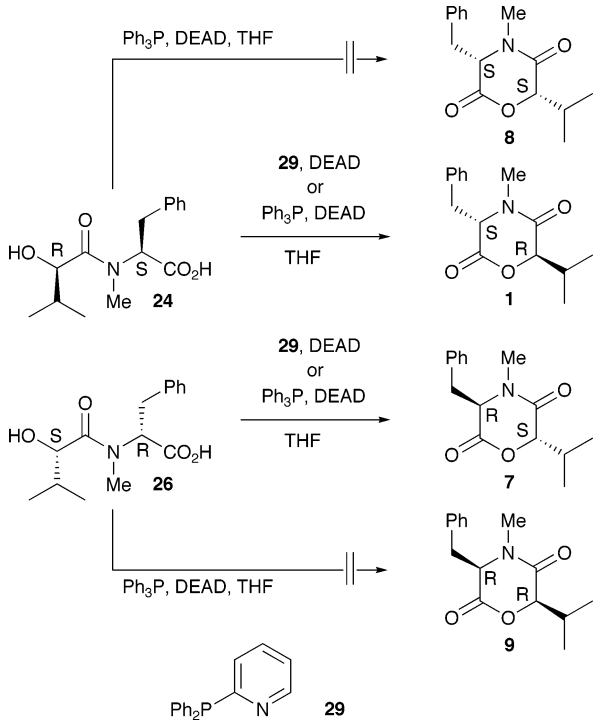


TABLE 1. Variation of Chemical Yields of Compounds 15–18, 20, and 21 with Coupling Reagent

amide	PyBrop yield (%)	HATU yield (%)	R	R^1	hydrolysis product	hydrolysis yield (%)
15	38	76	^{i}Pr (R)	Bn (S)	**24**	54
16	41	73	^{i}Pr (S)	Bn (S)	**25**	53
17	41	70	^{i}Pr (S)	Bn (R)	**26**	51
21		65	^{i}Pr (R)	Bn (R)	**27**	51
18		68	Bn (R)	^{i}Pr (S)	**19**	53
18 + **20**		27 + 15[a]	Bn (S)	^{i}Pr (S)		

[a] This ratio determined from ^{1}H NMR integral ratios of the acidic hydrolysis product mixture.

SCHEME 5



byproduct **28**. This problem was largely overcome through the use of diphenyl(2-pyridyl)phosphine **29**,[16] which could be removed in the workup by an aqueous acid wash. The residue from the workup was then easier to purify by column chromatography. The isolated compounds **1** (50%) and **7** (52%) were the products of Mitsunobu cyclization with retention of configuration.

The Mitsunobu reaction normally proceeds with inversion of configuration. However, the occurrence of Mitsunobu reaction products showing retention of configuration has been reported. These reports indicate there are several factors that can influence the stereochemical course of the Mitsunobu reaction such as the electronic nature of the phosphine,[17,18] stereofacial hindrance in allylic substrates,[19] potential neighboring group participation,[20] the influence of added base,[19] and most commonly, the use of sterically hindered substrates.[21–23] Consequently, the Mitsunobu reaction mechanism has been the subject of several studies[18,24–26] and continuing debate. It was apparent the present alcohols **24** and **26** were also examples of hindered secondary alcohols.

The Mitsunobu reaction mechanism has been much studied.[17,18,21,23–26] These studies have shown the mechanism is as shown in Scheme 6. The mechanism shown in this scheme applies commonly to most intermolecular Mitsunobu reactions and unhindered Mitsunobu cyclizations where inversion of configuration of the substrate alcohol is observed.

However, in the case of hindered alcohols in Mitsunobu cyclizations (no base added[21]), the phosphorus transfer to the alkoxide either never occurs or the rate of transfer is inferior to the rate of attack by the alkoxide **30** on the acyl carbon of the acyloxyphosphonium ion **31**. This results in the formation of the expected ester **32** but with retention of configuration.

The hydroxyacids **25** and **27** held a yet greater surprise. When the Mitsunobu cyclization was conducted in the same manner as that in Scheme 5, the expected cycles **8** and **9** formed with retention of configuration, in 60% and 54% yields, respectively, provided the rate of addition was slow (over 1–2 h) (Scheme 7). In the course of reaction optimization, the rate of addition of the hydroxyacid was varied. When the hydroxyacid addition was performed over a 10-min period (fast) the reaction gave the morpholines **7** and **1** in 52% and 30% yield, respectively. To the best of our knowledge this is the first example of a Mitsunobu cyclization that has a different stereochemical outcome depending on the rate of addition of the substrate. We attribute this divergent behavior to the effective concentration of the reactive functional

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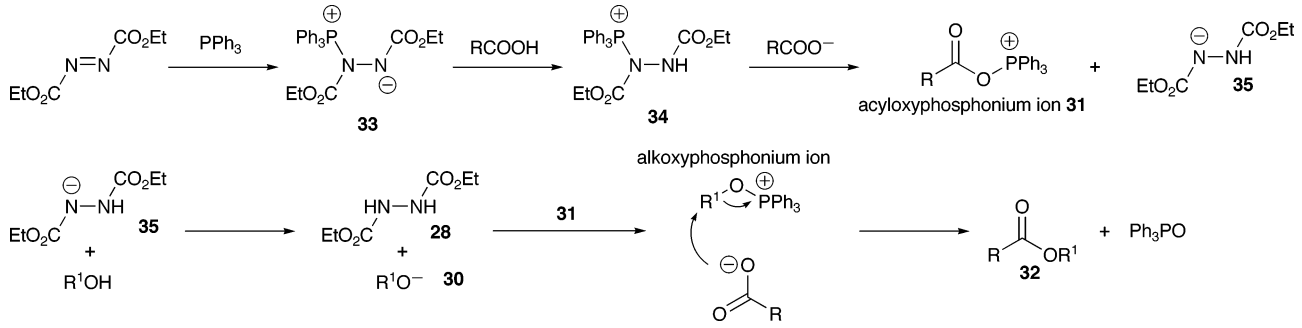
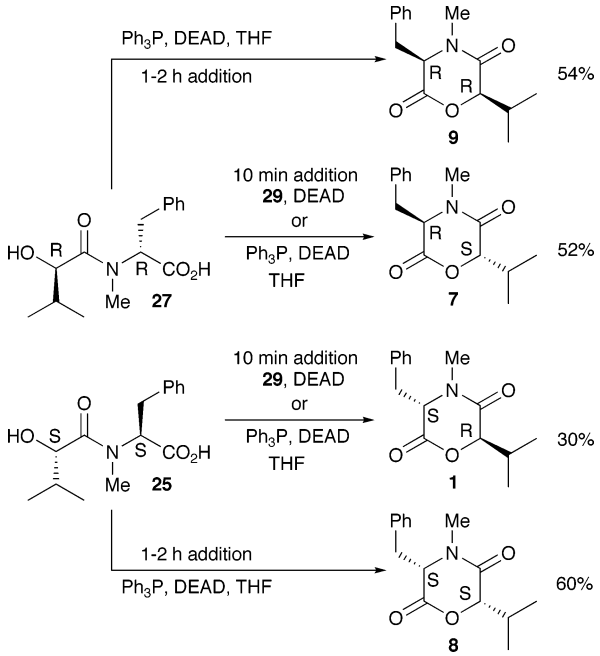
(26) Camp, D.; Jenkins, I. D. *Aust. J. Chem.* **1992**, *45*, 47.

SCHEME 6. Mitsunobu Reaction Mechanism



SCHEME 7



groups, the carboxylic acid, and the alcohol, and the possibility of an intermolecular process occurring with fast addition of the substrate.

To explain the course of the reactions in Scheme 7, Scheme 8 shows a suggested mechanism for the Mitsunobu cyclization of the *R*,*R*-hydroxy acid **27** when the substrate was added slowly (1−2 h) to a preformed solution of the betaine **33**. The mechanism of this reaction follows that described above for the *R*,*S*- and *S*,*R*-hydroxyacids **24** and **26**.

The *R*,*R*-hydroxyacid **27** gave a different Mitsunobu product when the substrate was added rapidly (over 10 min) to the betaine **33** solution (Scheme 9). Initially, it is deprotonated to form the carboxylate **36** and then the acyloxyphosphonium ion **37** forms. Since the carboxylate concentration was higher due to the rapid substrate addition, we propose that remaining carboxylate **36** is able to intercept the phosphonium ion **37** and form an anhydride **38**. Anhydride formation in the Mitsunobu reaction has been observed.[23,25,27]

At this point deprotonation of the alcohol **37** and cyclization of the alkoxide can be discounted as that path would give the morpholine-2,5-dione **9**, which was not isolated. Transfer of the phosphorus to the alkoxide can also be discounted as this did not occur in the previous reactions (Scheme 5) when the concentration of the phosphorylating species **34** was relatively higher.

The alkoxide **39**, formed from the diol **38**, is less reactive than the acyloxyphosphonium ion **37**. This is evident from the fact that the alkoxide **39** does not cyclize onto the anhydride and so does not give the Mitsunobu product **9**. Thus the alkoxide **39** was available for phosphorylation to give the alkoxyphosphonium ion **40**. A carboxylate ion **36** then reacts with the alkoxyphosphonium ion **40** to generate a new anhydride **38** and the activated carboxylate **41**, which cyclizes to give the morpholine-2,5-dione **7** in 52% yield. The *S*,*S*-hydroxy acid **25**, under the same conditions, gave the morpholine-2,5-dione **1** in 30% yield.

Scheme 9 proposes the anhydride **38** as a key intermediate in the Mitsunobu reaction to form compound **7**. Anhydrides have been isolated by other workers[23,27] from Mitsunobu reactions and so attempts were made to identify similar intermediates in the current work. Accordingly, the carboxylic acid **12a** was submitted to reaction under Mitsunobu conditions to form the anhydride **42** (Scheme 10). No evidence for the presence of the anhydride was found and the anhydride **42** was not isolated from the reaction. In a second attempt, the carboxylic acid **43** was also treated with triphenylphosphine and DEAD in THF solution but no anhydride **44** was isolated, only starting material **43** was present by TLC analysis.

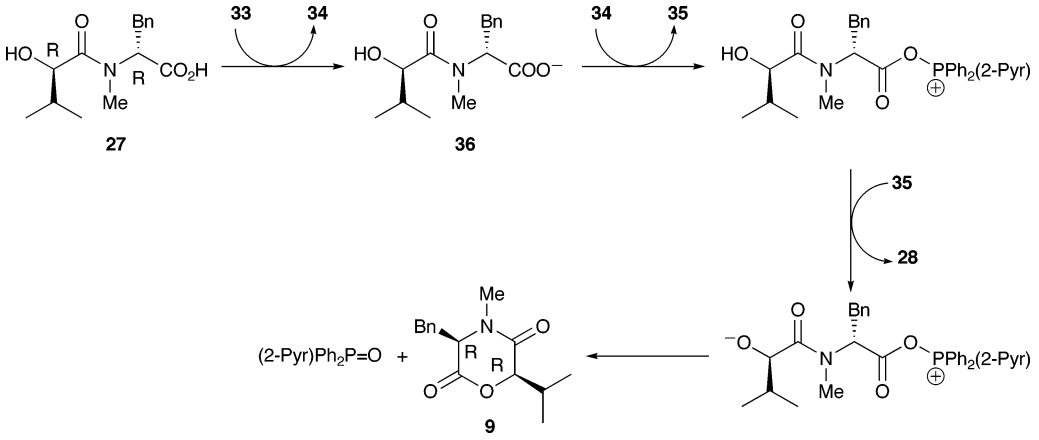
An analysis of the Mitsunobu cyclization results from Scheme 7 suggested that epimerization of an initial or kinetic product was generating the inverted or thermodynamic products **1** and **7** from the *S*,*S*- or *R*,*R*-precursors **25** or **27**, respectively. Accordingly, though this seemed unlikely, the *S*,*S*-depsipeptide **8** was added over 10 min to a premixed solution of **29** and DEAD. The *S*,*S*-depsipeptide **8** was isolated unchanged from this reaction. It was concluded from this result that epimerization was not occurring in the Mitsunobu cyclizations of substrates **25** and **27**.

It should also be noted that all the Mitsunobu reactions described herein were performed without addition of an amine base. McNulty et al.[21] have found this amine addition can facilitate the transfer of the phosphorus from the initial acyloxyphosphonium ion to the alkoxyphosphonium ion resulting in increased yields of the usual, inverted configuration product.

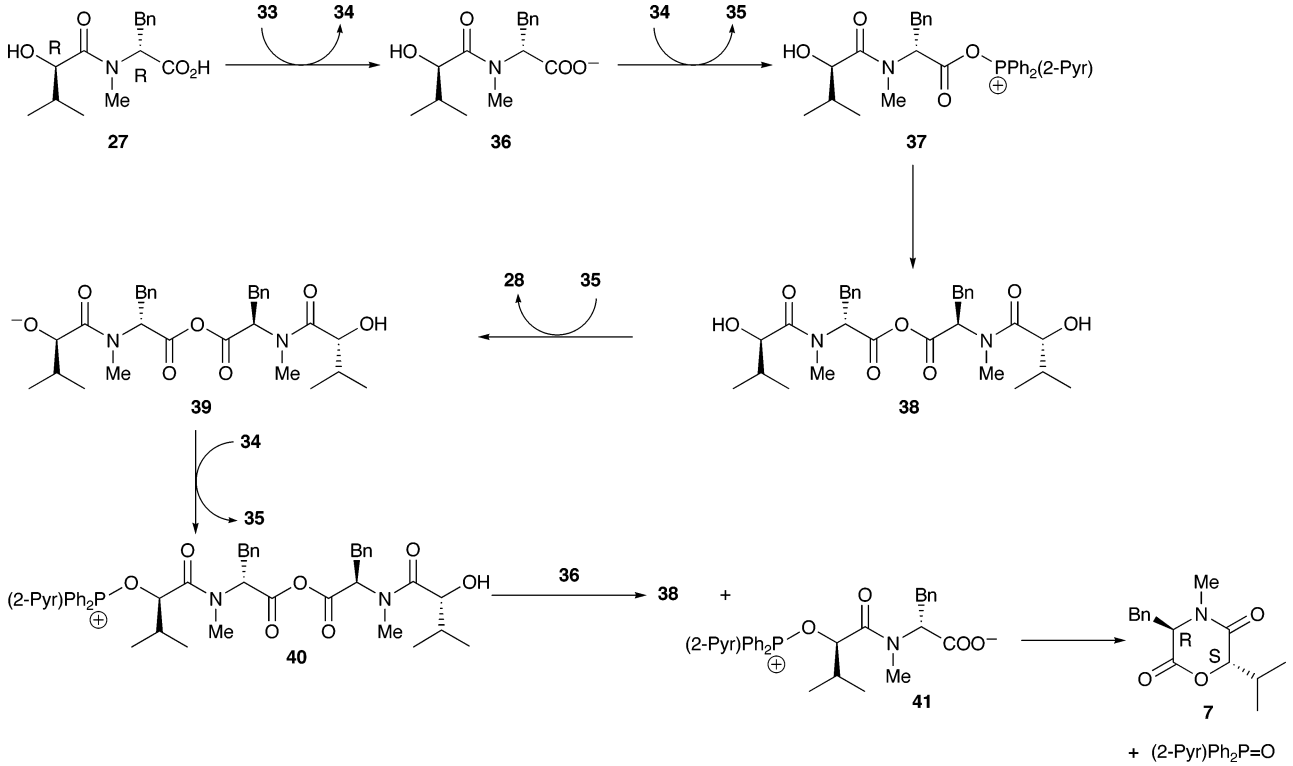
In the next part of this study the regioisomeric morpholinediones **10** and **11** were studied. Accordingly, the

(27) Harvey, P. J.; von Itzstein, M.; Jenkins, I. D. *Tetrahedron* **1997**, *53*, 3933.

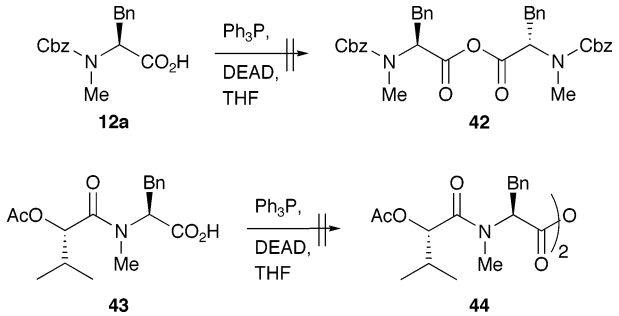
SCHEME 8. Mechanism of Mitsunobu Cyclization of Substrate 27 under Slow Addition/Low Concentration Reaction Conditions



SCHEME 9. Mechanism of Mitsunobu Cyclization of Substrate 27 under Fast Addition/High Concentration Reaction Conditions



SCHEME 10. Attempted Formation of Anhydride Intermediates in Mitsunobu Reactions



diester **18** was deprotected to give the cyclization precursor **19** (Scheme 11). Mitsunobu cyclization of compound **19** afforded the morpholinedione **10** (50% yield). Compound **10** is the result of Mitsunobu cyclization with retention of configuration. Proof that cyclization with retention was the path the reaction was following was more difficult as the product was a novel compound. To confirm the reaction result, the hydroxy-acid **19** was cyclized by lactonization with dicyclohexylcarbodiimide (DCC) and 4-*N*,*N*-(dimethylamino)pyridine (DMAP). This gave a 53% yield of a morpholinedione, which had a ^{1}H NMR spectrum identical with that of the material from the Mitsunobu cyclization. It is assumed the DCC/DMAP lactonization proceeds without epimerization of the alkoxy carbon. Thus, the Mitsunobu cyclization of compound **19** can be classified as the cyclization of a hindered alcohol of the same type as depicted in Scheme 5.

It was hoped the sequence, generating compound **11**, would be analogous to that in Scheme 7. However, as

SCHEME 11

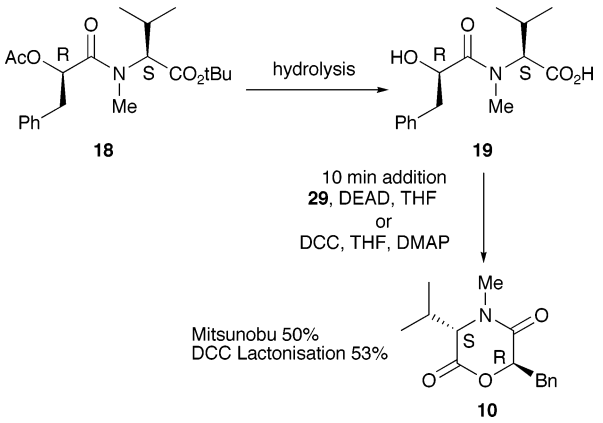


Table 1 indicates, the yield of the required amide **20**, which would give the Mitsunobu precursor after hydrolysis, was disappointingly low due to epimerization in the coupling reaction. Since samples of amide **20** were not readily available, further efforts toward compound **11** were abandoned.

Conclusion

Kagamizono et al.[9] succeeded in preparing Bassiatin **1** and its stereoisomers **7**, **8**, and **9** using two different synthetic sequences (Scheme 1). The overall yields for the reactions shown in Scheme 1 are 23% and 16% for Bassiatin **1**; 31% and 15% for the enantiomer **7**; 10% for the *S*,*S*-stereoisomer **8**; and 16% for the *R*,*R*-stereoisomer **9**. In comparison, the work described herein cannot claim substantial improvements on those yields. The two routes to Bassiatin **1** were completed in 15% and 9% overall yields. Both the sequences to the Bassiatin enantiomer **7** gave 13% overall yield. The synthesis of compound **8** from *N*-methyl phenylalanine **14a** proceeded in 18% yield while compound **9** was isolated in 13% yield from compound **14b**.

Contrary to initial plans and expectations, the Mitsunobu cyclizations of precursors **24** and **26** proceeded with retention of configuration. This result was observed for both substrates irrespective of the rate of their addition to the reaction. This result led to the conclusion that the substrates should be classified as hindered and were reminiscent of compounds studied by De Brabander et al.[22] and De Shong et al.[23] A mechanistic rationale for the retention of configuration is presented in Scheme 6 and this rationale agrees with the general conclusions of De Shong et al.[23] and Jenkins et al.[25] and McNulty et al.[21]

In the next phase of the study, the *R*,*R*- and *S*,*S*-precursors **25** and **27** were submitted to Mitsunobu cyclization. When the substrates **25** and **27** were added to premixed solutions of DEAD and diphenyl(2-pyridyl)-phosphine **29** over 1−2 h, the reaction gave the morpholine-2,5-diones **8** and **9**, respectively, exhibiting retention of configuration. These results are in accord with the mechanism in Scheme 6. The same reactions were then conducted except that the substrate addition was over 10 min. This simple change led to isolation of the products of Mitsunobu cyclization with inversion of configuration, namely Bassiatin **1** and its enantiomer **7**.

The results of all these Mitsunobu reactions are in accord with the literature values for ^{1}H and ^{13}C NMR spectra of Bassiatin and its stereoisomers. All the synthetic products match the spectra and physical properties of the literature compounds. A mechanistic explanation for the divergent behavior of the *S*,*S*- and *R*,*R*-precursors **25** and **27** in the Mitsunobu cyclization is presented in Schemes 8 and 9.

In efforts to ascertain the generality of the observations described above, synthesis of the regioisomeric morpholinediones **10** and **11** was attempted. Compound **10** was prepared via a Mitsunobu reaction that proceeded with retention of configuration, which is the same outcome as found for precursors **24** and **26**. Thus it would seem the level of steric hindrance present in the substrates studied[19−21,23] and herein is generally sufficient to alter the course of the Mitsunobu reaction mechanism. Efforts to make compound **11** were frustrated by epimerization in the amide coupling reaction and were abandoned.

We believe the Mitsunobu reactions described for substrates **25** and **27** represent the first examples of a novel effect of concentration with regard to the course of the Mitsunobu cyclization.

Experimental Section

General Procedure for the Synthesis of *tert*-Butyl Esters 13a, 13b, and 13c. The acid (1.0 g, 3.2 mmol) and $(Boc)_2O$ (849 mg, 3.8 mmol) were dissolved in dry *tert*-butyl alcohol (10 mL). To this solution was added DMAP (47 mg, 0.4 mmol) and the reaction was left to stir under N_2 at room temperature for 4−24 h (monitored via TLC). The reaction mixture was concentrated under reduced pressure and the residue was dissolved in ethyl acetate (100 mL) and the organic solution was washed with saturated sodium bicarbonate solution (3 × 30 mL). The organic phase was dried ($MgSO_4$) and concentrated in vacuo. The crude residue was purified by flash column chromatography, eluting with 10% ethyl acetate/hexane.

Data for Compound 13a. Colorless solid, yield (90%). $[\alpha]^{23}_D$ −43.8 (*c* 1.0, CH_2Cl_2). Anal. Calcd for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.40; H, 7.42; N, 3.60. FTIR (NaCl) ν 3065, 3031, 2978, 1732, 1705, 1606, 1497, 1455, 1400, 1369, 1311, 1257, 1157, 1082, 1030, 991, 848, 738, 699 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, rotamers) δ 7.33−7.12 (m, 10H), 5.23−4.96 (m, 2H), 4.96−4.90 (m, 0.5H), 4.75 (dd, 0.5H, J = 5.0, 4.9 Hz), 3.35−3.22 (1H, m), 3.06−2.93 (m, 1H), 2.86−2.82 (m, 3H), 1.44 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$, rotamers) δ 170.0, 169.7, 156.4, 155.9, 137.3, 136.7, 136.4, 128.7, 128.2, 127.7, 127.6, 127.4, 126.4, 126.3, 126.1, 81.6, 81.5, 67.1, 66.8, 61.0, 60.7, 35.1, 34.8, 31.7, 31.4, 27.8.

Data for Compound 13b. Colorless solid, yield (90%). $[\alpha]^{23}_D$ +46.1 (*c* 1.0, CH_2Cl_2). Anal. Calcd for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.46; H, 7.42; N, 3.81. FTIR (NaCl) ν 3033, 2980, 2942, 1727, 1710, 1603, 1499, 1459, 1421, 1397, 1371, 1329, 1239, 1120, 1029, 975, 906, 839, 797, 776, 738, 698 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, rotamers) δ 7.35−7.12 (m, 10H), 5.15−4.96 (m, 2H), 4.96−4.90 (m, 0.5 H), 4.75 (dd, 0.5H J = 5.1, 5.1 Hz), 3.35−3.22 (m, 1H), 3.06−2.93 (m, 1H), 2.86−2.82 (m, 3H), 1.44 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$, rotamers) δ 170.0, 169.7, 156.4, 155.9, 137.3, 136.7, 136.4, 128.7, 128.5, 128.3, 128.2, 127.7, 127.6, 127.4, 126.4, 126.3, 81.6, 81.5, 67.0, 66.8, 61.0, 60.7, 35.0, 34.8, 31.7, 31.4, 27.8.

Data for Compound 13c. Colorless solid, yield 90%. $[\alpha]^{24}_D$ −26.2 (*c* 1.0, CH_2Cl_2). Anal. Calcd for $C_{22}H_{27}NO_4$: C, 67.26; H, 8.47; N, 4.36. Found: C, 67.32; H, 8.49; N, 4.19. FTIR (NaCl) ν 3067, 3035, 2971, 2877, 1731, 1705, 1455, 1402, 1370, 1306, 1216, 1142, 1050, 1030, 986, 863, 795, 769, 736, 698 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, rotamers) δ 7.34−7.24 (m,

5H), 5.23−5.06 (m, 2H), 4.37 (d, 0.5H, J = 10.4 Hz), 4.16 (d, 0.5H, J = 10.6 Hz), 2.88 (s, 3H), 2.19−2.07 (m, 1H), 1.42−1.40 (m, 9H), 0.99−0.83 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$, rotamers) δ 170.3, 169.9, 156.9, 155.3, 136.7, 128.3, 127.8, 127.5, 127.4, 81.24, 81.2, 67.1, 67.1, 65.1, 64.6, 30.11, 30.1, 27.9, 27.6, 27.4, 19.5, 18.9.

General Procedure for Synthesis of the α-Acetoxy Acids 5a−d.[13] $NaNO_2$ (5.52 g, 80 mmol) was added portionwise to a solution of the amino acid **14** (5.0 g, 40 mmol) in acetic acid (60 mL). The solution was cooled intermittently with an ice bath to keep the reaction mixture near room temperature. Once the addition was complete, the mixture was left to stir at room temperature for 24 h. The solvent was then removed in vacuo, the residue was dissolved in ether (150 mL), and the ethereal solution was washed with water (3 × 40 mL). The organic layer was extracted with saturated $NaHCO_3$ solution (3 × 40 mL). The aqueous extracts were then acidified with 2 N HCl and extracted with ether (3 × 40 mL). The combined organic layers were dried ($MgSO_4$) and reduced in vacuo to give the required α-acetoxy acid.

Data for Compound 5a. Yellow oil, yield 73%. FTIR (NaCl) ν 3585−2880, 2972, 2882, 1746, 1731, 1645, 1470, 1375, 1236, 1132, 1113, 1039, 978, 915, 734 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.06 (br s, 1H), 4.81 (d, 1H, J = 4.3 Hz), 2.23−2.14 (m, 1H), 2.08 (s, 3H), 0.96 (d, 3H, J = 5.3 Hz), 0.93 (d, 3H, J = 5.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.1, 171.0, 76.2, 29.8, 20.3, 18.5, 16.9. A small portion was converted to the *tert*-butyl amine salt. Mp 139 °C. $[\alpha]^{26}_D$ −43.7 (c 1.0, $CHCl_3$). Anal. Calcd for $C_{11}H_{23}NO_4$: C, 55.63; H, 9.94; N, 6.00. Found: C, 55.59; H, 9.99; N, 5.97.

Data for Compound 5b. Yellow oil, yield 75%. FTIR (NaCl) ν 3700−2880, 2972, 1730, 1650, 1469, 1375, 1236, 1132, 1113, 1038, 914, 858, 734 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.20 (br s, 1H), 4.80 (d, 1H, J = 4.1 Hz), 2.22−2.16 (m, 1H), 2.07 (s, 3H), 0.95 (d, 3H, J = 5.9 Hz), 0.93 (d, 3H, J = 6.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.5, 171.2, 76.3, 29.7, 20.3, 18.5, 17.0. A small portion was converted to the *tert*-butyl amine salt. Mp 138 °C. $[\alpha]^{25}_D$ +40.5 (c 1.0, $CHCl_3$). Anal. Calcd for $C_{11}H_{23}NO_4$: C, 55.63; H, 9.94; N, 6.00. Found: C, 55.64; H, 9.89; N, 6.03.

Data for Compound 5c. This compound was identical with material previously described.[12] The optical purity was determined by hydrolysis of the acetate to give *R*-2-hydroxy-3-phenylpropanoic acid.[28]

Data for Compound 5d. This compound was identical with material previously described.[12] The optical purity was determined by hydrolysis of the acetate to give *S*-2-hydroxy-3-phenylpropanoic acid.[28]

General Coupling Procedure To Form Amides 15−18 and 21. Method 1: PyBrop Coupling. The acid (3.1 mmol), the amine (3.4 mmol), and PyBrop (1.73 g, 3.72 mmol) were taken up in dry dichloromethane (3.1 mL). This solution was cooled to 0 °C in an ice bath. Diisopropylethylamine (1.6 mL, 9.4 mmol) was then added to the reaction mixture. The reaction was left to stir at 0 °C for 2 h, then at room temperature for 3 h. After this time, excess ethyl acetate (25 mL) was added and the organic solution was washed with saturated sodium bicarbonate solution (3 × 10 mL), then dilute citric acid solution (3 × 10 mL). The organic layer was dried ($MgSO_4$) and filtered and the filtrate was evaporated at reduced pressure. The residual crude material was purified by flash chromatography eluting with 20% ethyl acetate−hexane to afford the pure title amide.

Method 2: HATU Coupling. The acid (500 mg, 3.1 mmol), the amine (808 mg, 3.4 mmol), and HATU (1.4 g, 3.8 mmol) were dissolved in dry CH_2Cl_2 (3.4 mL). The reaction mixture was cooled to 0 °C. To the stirring solution was added DIPEA (1.6 mL, 9.4 mmol). The reaction was stirred for 2 h at 0 °C. The reaction mixture was then passed through a short silica plug eluting with 20% ethyl acetate−hexane. The solvent was reduced in vacuo and the crude material was purified via flash chromatography eluting with 20% ethyl acetate−hexane.

Data for Amide 15. Colorless solid, yield (PyBrop 38%; HATU 76%). Anal. Calcd for $C_{21}H_{31}NO_5$: C, 66.82; H, 8.28; N, 3.71. Found: C, 66.90; H, 8.31; N, 3.84. Mp 50−52 °C. $[\alpha]^{25}_D$ −53.8 (c 0.5, CH_2Cl_2). FTIR (KBr) ν 3063, 3036, 2958, 1731, 1654, 1548, 1447, 1370, 1230, 1160, 1060, 1039, 989, 909, 847, 750, 680, 574 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, rotamers) δ 7.24−7.10 (m, 5H), 5.11 and 5.07 (each d, 0.5H, J = 4.7 Hz), 4.87 (d, 1H, J = 6.0 Hz), 3.27 (dd, 1H, J = 4.7, 14.7 Hz), 2.95−2.86 (m, 1H), 2.83 (s, 3H), 2.01 (s, 3H), 1.80−1.69 (m, 1H), 1.40 (s, 8H), 1.31 (s, 1H), 0.89 (d, 0.5H, J = 6.6 Hz), 0.81 (d, 0.5H, J = 6.8 Hz), 0.65 (d, 2.5H, J = 6.7 Hz), 0.59 (d, 2.5H, J = 6.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, rotamers) 170.5, 170.3, 169.6, 169.3, 168.8, 137.2, 136.4, 129.2, 128.7, 128.4, 128.3, 128.0, 126.7, 126.4, 82.3, 81.6, 74.5, 61.8, 59.4, 36.2, 34.4, 32.5, 30.1, 29.4, 27.7, 27.6, 20.4, 20.3, 18.5, 18.0, 17.6, 17.0.

Data for Amide 16. Colorless oil, yield (PyBrop 41%; HATU 73%). Anal. Calcd for $C_{21}H_{31}NO_5$: C, 66.82; H, 8.28; N, 3.71. Found: C, 67.00; H, 8.58; N, 3.72. $[\alpha]^{19}_D$ −77.0 (c 0.5, CH_2Cl_2). FTIR (NaCl) ν 3064, 3030, 2975, 2877, 1733, 1663, 1455, 1415, 1393, 1370, 1240, 1157, 1092, 1034, 913, 845, 739, 700 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, rotamers) δ 7.28−7.13 (m, 5H), 5.29 and 5.25 (each d, 0.5H, J = 6.1 Hz), 4.96 (d, 1H, J = 7.5 Hz), 3.28 (dd, 1H, J = 6.0, 14.4 Hz), 2.96 (s, 3H), 2.92−2.88 (m, 1H), 2.18−2.07 (m, 1H), 2.00 (s, 3H), 1.56−1.40 (m, 9H), 0.97−0.42 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$, rotamers) 170.4, 170.2, 169.8, 169.7, 137.1, 136.9, 129.1, 128.8, 128.5, 128.2, 127.1, 126.4, 82.6, 81.8, 74.4, 74.0, 62.0, 59.0, 35.3, 34.6, 32.5, 31.9, 29.9, 29.8, 29.5, 27.9, 20.6, 20.5, 18.6, 18.4, 18.2, 17.8, 17.2.

Data for Amide 17. Colorless solid, yield (PyBrop 41%; HATU 70%). Anal. Calcd for $C_{21}H_{31}NO_5$: C, 66.82; H, 8.28; N, 3.71. Found: C, 66.78; H, 8.32; N, 3.75. Mp 55−57 °C. $[\alpha]^{23}_D$ +50.4 (c 0.5, CH_2Cl_2). FTIR (KBr) ν 3081, 2953, 2913, 1723, 1661, 1453, 1368, 1225, 1175, 1023, 850, 819, 790, 748, 694, 626, 557, 522 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, rotamers) δ 7.26−7.14 (m, 5H), 5.18 and 5.14 (each d, 0.5H, J = 4.8 Hz), 4.92 (d, 1H, J = 6.1 Hz), 3.33 (dd, 1H, J = 4.8, 14.7 Hz), 2.99−2.90 (m, 1H), 2.89 (s, 3H), 2.07 (s, 2.5H), 2.05 (s, 0.5H), 1.88−1.73 (m, 1H), 1.45 (s, 8H), 1.36 (s, 1H), 0.93 (d, 0.5H, J = 6.7 Hz), 0.86 (d, 0.5H, J = 6.9 Hz), 0.70 (d, 2.5H, J = 6.7 Hz), 0.63 (d, 2.5H, J = 6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, rotamers) 170.6, 169.8, 169.5, 137.4, 129.4, 128.9, 128.6, 128.5, 126.9, 126.6, 81.8, 74.6, 62.0, 59.5, 36.4, 34.6, 32.7, 30.3, 29.6, 27.9, 27.8, 20.6, 18.7, 18.4, 17.8, 17.2.

Data for Compound 18. Colorless solid, yield 68%. Mp 40−43 °C. $[\alpha]^{25}_D$ −74.2 (c 1.0, CH_2Cl_2). Anal. Calcd for $C_{21}H_{31}NO_5$: C, 66.82; H, 8.28; N, 3.71. Found: C, 66.91; H, 8.28; N, 3.74. FTIR (NaCl) ν 2972, 2934, 1742, 1665, 1456, 1413, 1370, 1238, 1160, 1138, 1061, 1034, 747, 701 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, rotamers) δ 7.30−7.20 (m, 5H), 5.52−5.43 (m, 1H), 4.62 (d, 0.6H, J = 10.5 Hz), 3.97 (d, 0.4H, J = 10.6 Hz), 3.16−3.06 (m, 2H), 2.94−2.92 (m, 3H), 2.32−2.24 (m, 1H), 2.05−2.01 (m, 3H), 1.46−1.41 (m, 9H), 1.02−0.61 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$, rotamers) δ 170.5, 170.3, 170.0, 169.0, 136.9, 134.9, 129.4, 129.3, 128.6, 128.5, 82.6, 81.4, 71.5, 71.2, 66.8, 63.0, 37.5, 37.2, 31.2, 29.1, 28.0, 28.0, 27.9, 27.5, 27.2, 20.6, 19.8, 19.7, 19.6, 18.8, 18.7.

Data for Amide 21. Colorless oil, yield 65%. $[\alpha]^{23}_D$ +68.6 (c 0.5, CH_2Cl_2). Anal. Calcd for $C_{21}H_{31}NO_5$: C, 66.82; H, 8.28; N, 3.71. Found: C, 66.76; H, 8.30; N, 3.74. FTIR (NaCl) ν 3029, 2975, 2933, 2877, 1735, 1661, 1496, 1455, 1413, 1392, 1370, 1343, 1240, 1157, 1092, 1033, 740, 700, 669 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, rotamers) δ 7.28−7.13 (m, 5H), 5.29 and 5.26 (each d, 0.5H, J = 6.1 Hz), 4.97 (d, 1H, J = 7.5 Hz), 3.28 (dd, 1H, J = 14.4, 6.1 Hz), 2.96 (s, 3H), 2.92−2.88 (m, 1H), 2.16−2.04 (m, 1H), 2.00 (s, 3H), 1.45−1.41 (m, 9H), 0.97−0.43 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$, rotamers) δ 170.6, 170.0, 169.8, 137.5, 137.0, 129.6, 129.0, 128.6, 128.5, 126.8, 126.6,

(28) The synthetic compound was compared with commercial material available from the Aldrich Chemical Co.

82.0, 81.8, 74.9, 62.0, 59.5, 36.4, 34.6, 32.7, 30.3, 29.6, 28.0, 27.9, 20.6, 18.8, 18.4, 17.8, 17.2.

General Procedure for Deprotection of the Amides 15−18 and 21. The amide (300 mg, 1.1 mmol) was dissolved in dioxane (3 mL) and 2 N hydrochloric acid (3 mL) was added. The reaction mixture was left to stir at 60 °C for 30 h. The reaction was then allowed to cool to room temperature and then diluted with water (20 mL). The aqueous mixture was extracted with ethyl acetate (2 × 10 mL). The combined extracts were washed with saturated brine (2 × 10 mL). The organic phase was dried ($MgSO_4$), filtered, and evaporated in vacuo. The residual oil was purified by flash chromatography eluting with dichloromethane:methanol:acetic acid 99.4:0.5:0.1 to afford the hydroxy acid.

Data for Amide 19. Colorless oil, yield 53%. $[\alpha]^{23}_D$ +83.6 (*c* 0.83, EtOH). FTIR (NaCl) ν 3031, 2968, 2835, 1748, 1668, 1496, 1455, 1406, 1372, 1300, 1245, 1114, 1071, 843, 753, 666 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.33−7.27 (m, 5H), 5.04 (dd, 1H, J = 3.7, 6.6 Hz), 3.64 (d, 1H, J = 6.1 Hz), 3.43 (dd, 1H, J = 3.5, 14.5 Hz), 3.18 (dd, 1H, J = 6.9, 14.9 Hz), 2.94 (s, 3H), 2.23−2.14 (m, 1H), 1.08 (d, 3H, J = 6.8 Hz), 0.99 (d, 3H, J = 6.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.2, 165.1, 135.6, 130.0, 128.6, 127.0, 78.2, 67.4, 37.7, 34.4, 31.7, 19.6, 18.3.

Data for Amide 24. Colorless solid, yield 54%. Mp 135−137 °C. $[\alpha]^{23}_D$ +183.0 (*c* 0.5, CH_2Cl_2). FTIR (NaCl) ν 3476, 2970, 2939, 2875, 1749, 1652, 1498, 1460, 1408, 1368, 1257, 1127, 1041, 964, 926, 880, 825, 767, 708, 655, 595 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.31−7.28 (m, 3H), 7.10−7.07 (m, 2H), 4.37 (t, 1H, J = 4.3 Hz), 3.24 (dd, 1H, J = 4.1, 14.0 Hz), 3.15 (dd, 1H, J = 4.2, 14.0 Hz), 2.98 (s, 3H), 2.97 (d, 1H, J = 3.1 Hz), 2.31−2.21 (m, 1H), 0.80 (d, 3H, J = 7.1 Hz), 0.72 (d, 3H, J = 6.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) 167.1, 165.4, 134.0, 129.6, 129.0, 128.0, 81.1, 62.6, 36.9, 32.3, 29.5, 18.4, 15.0.

Data for Amide 25. Colorless oil, yield 53%. $[\alpha]^{24}_D$ −46.6 (*c* 0.5, CH_2Cl_2). FTIR (NaCl) ν 3464, 3032, 2968, 2937, 2876, 1746, 1667, 1497, 1456, 1406, 1377, 1341, 1282, 1252, 1200, 1181, 1136, 1043, 757, 702 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, rotamers) δ 7.32−7.23 (m, 3H), 7.15−7.12 (m, 2H), 4.37 (t, 1H, J = 4.9 Hz), 4.33 (d, 1H, J = 7.1 Hz), 3.32 (dd, 1H, J = 4.8, 14.1 Hz), 3.26 (dd, 1H, J = 4.2, 13.5 Hz), 2.96 (s, 3H), 1.23−1.12 (m, 1H), 0.83 (d, 3H, J = 6.8 Hz), 0.57 (d, 3H, J = 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) 165.9, 164.5, 134.7, 129.8, 129.0, 128.6, 127.8, 83.8, 61.9, 38.0, 32.8, 32.4, 18.8, 17.4.

Data for Amide 26. Colorless solid, yield 51%. Mp 124−126 °C. $[\alpha]^{24}_D$ −180.9 (*c* 0.5, CH_2Cl_2). FTIR (NaCl) ν 3464, 3031, 2936, 2876, 1749, 1654, 1498, 1461, 1409, 1367, 1341, 1257, 1204, 1168, 1083, 1042, 961, 926, 879, 807, 768, 708, 656, 592, 545 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.31−7.24 (m, 3H), 7.12−7.09 (m, 2H), 4.38 (t, 1H, J = 4.3 Hz), 3.26 (dd, 1H, J = 4.1, 14.0 Hz), 3.17 (dd, 1H, J = 4.6, 14.0 Hz), 3.00 (s, 3H), 2.99 (s, 1H), 2.33−2.23 (m, 1H), 0.82 (d, 3H, J = 7.1 Hz), 0.74 (d, 3H, J = 6.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) 167.2, 165.5, 134.1, 129.7, 128.2, 127.2, 81.2, 62.7, 37.1, 32.4, 29.7, 18.5, 15.1.

Data for Amide 27. Colorless oil, yield 51%. $[\alpha]^{24}_D$ −46.0 (*c* 0.5, CH_2Cl_2). FTIR (NaCl) ν 3449, 2967, 2933, 2877, 1746, 1665, 1497, 1456, 1406, 1377, 1341, 1282, 1253, 1201, 1182, 1137, 1043, 758, 703 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.30−7.21 (m, 3H), 7.15−7.12 (m, 2H), 4.37 (apparent t, 1H, J = 4.5 Hz), 4.33 (d, 1H, J = 7.1 Hz), 3.32 (dd, 1H, J = 13.4, 4.6 Hz), 3.26 (dd, 1H, J = 13.5, 4.4 Hz), 2.96 (s, 3H), 1.24−1.13 (m, 1H), 0.83 (d, 3H, J = 6.8 Hz), 0.58 (d, 3H, J = 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 164.5, 134.8, 129.8, 129.0, 127.8, 83.8, 61.9, 38.1, 32.9, 32.4, 18.8, 17.4.

Mitsunobu Cyclization of Compound 24: Fast Addition. Preparation of Bassiatin 1. To a premixed solution of **29** (170 mg, 0.65 mmol) and DEAD (100 μL, 0.65 mmol) in dry THF (22 mL) was added a solution of the depsipeptide **24** (150 mg, 0.5 mmol) in dry THF (8 mL) over 10 min. During this period the reaction temperature was maintained at 0 °C, followed by stirring at room temperature for 18 h. The reaction mixture was then concentrated at reduced pressure and the residue was purified by flash chromatography eluting with 80:20:0.1 ether−hexane−Et_3N.

Data for Compound 1. Colorless solid, yield 50%. Mp 145−146 °C. $[\alpha]^{22}_D$ +165.9 (*c* 1.0, CH_2Cl_2). Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.86; H, 7.37; N, 5.38. FTIR (NaCl) ν 2968, 2939, 2875, 1746, 1650, 1497, 1460, 1409, 1368, 1256, 1169, 1131, 1083, 1042, 961, 926, 879, 824, 768, 707, 656, 599, 546 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.33−7.29 (m, 3H), 7.12−7.09 (m, 2H), 4.39 (apparent t, 1H, J = 4.4 Hz), 3.27 (dd, 1H, J = 14.0, 4.2 Hz), 3.17 (dd, 1H, J = 14.0, 4.5 Hz), 3.00 (s, 3H), 2.99 (d, 1H, J = 2.2 Hz), 2.33−2.24 (m, 1H), 0.82 (d, 3H, J = 7.1), 0.74 (d, 3H, J = 6.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2, 165.5, 134.1, 129.7, 129.2, 128.2, 81.2, 62.7, 37.1, 32.4, 29.6, 18.6, 15.1.

Mitsunobu Cyclization of Compound 24: Slow Addition. Preparation of Bassiatin 1. To a premixed solution of **29** (170 mg, 0.65 mmol) and DEAD (100 μL, 0.65 mmol) in dry THF (22 mL) was added a solution of the depsipeptide **24** (150 mg, 0.5 mmol) in dry THF (8 mL) over 2 h. During this period the reaction temperature was maintained at 0 °C, followed by stirring at room temperature for 18 h. The reaction mixture was then concentrated at reduced pressure and the residue was purified by flash chromatography eluting with 80:20:0.1 ether−hexane−Et_3N. The spectroscopic data for the product were the same as those for compound **1** above.

Mitsunobu Cyclization of Compound 26: Fast Addition. Preparation of Bassiatin Enantiomer 7. To a premixed solution of **29** (170 mg, 0.65 mmol) and DEAD (100 μL, 0.65 mmol) in dry THF (22 mL) was added a solution of the depsipeptide **26** (150 mg, 0.5 mmol) in dry THF (10 mL) over 10 min. During this period the reaction temperature was maintained at 0 °C, followed by stirring at room temperature for 18 h. The reaction mixture was then concentrated in vacuo. The oily residue was triturated with ethyl acetate−hexane to afford a solid, which was further purified via flash chromatography eluting with 70:30:0.1 ether−hexane−Et_3N to afford the depsipeptide **7**.

Data for Compound 7. Colorless solid, yield 52%. Mp 143−145 °C. $[\alpha]^{22}_D$ −160.0 (*c* 1.0, CH_2Cl_2). Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.88; H, 7.34; N, 5.42. FTIR (KBr) ν 2970, 2938, 1746, 1648, 1499, 1369, 1258, 1169, 1131, 1039, 964, 926, 879, 824, 766, 707, 599, 545 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.33−7.30 (m, 3H), 7.13−7.09 (m, 2H), 4.39 (apparent t, 1H, J = 4.3 Hz), 3.27 (dd, 1H, J = 14.0, 4.2 Hz), 3.18 (dd, 1H, J = 14.0, 4.5 Hz), 3.00 (s, 3H), 2.98 (d, 1H, J = 2.1 Hz), 2.34−2.24 (m, 1H), 0.82 (d, 3H, J = 7.1 Hz), 0.74 (d, 3H, J = 6.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2, 165.4, 134.1, 129.7, 129.1, 128.1, 81.2, 62.7, 37.0, 32.4, 29.6, 18.5, 15.1.

Mitsunobu Cyclization of Compound 25: Fast Addition. Preparation of Bassiatin 1. To a premixed solution of **29** (170 mg, 0.65 mmol) and DEAD (100 μL, 0.65 mmol) in dry THF (22 mL) was added a THF (8 mL) solution of the depsipeptide **25** (150 mg, 0.5 mmol) in dry THF (8 mL) over 10 min. During this period the reaction temperature was maintained at 0 °C, followed by stirring at room temperature for 18 h. The reaction mixture was then concentrated at reduced pressure and the residue was purified. The crude product was purified by flash chromatography eluting with 80:20:0.1 ether:hexane:Et_3N to afford the depsipeptide **1** as a colorless solid (39 mg, 30%) that was identical with material described above.

Mitsunobu Cyclization of Compound 25: Slow Addition. Preparation of Depsipeptide 8. To a premixed solution of **29** (170 mg, 0.65 mmol) and DEAD (100 μL, 0.65 mmol) in dry THF (22 mL) was added a solution of the amide **25** (150 mg, 0.5 mmol) in dry THF (8 mL) over 2 h. During this period the reaction temperature was maintained at 0 °C, followed by stirring at room temperature for 18 h. The reaction mixture was then concentrated in vacuo and the residue was purified by flash chromatography eluting with 80:20:0.1 ether:hexane:Et_3N to afford the compound **8** as a colorless oil (60% yield).

$[\alpha]^{21}_D$ −30.5 (*c* 1.0, CH_2Cl_2). FTIR (NaCl) *ν* 2968, 2937, 2877, 1745, 1666, 1497, 1455, 1406, 1377, 1341, 1282, 1252, 1200, 1137, 1043, 756, 702 cm^{-1}. HRMS (ES) *m/z* calcd for $C_{15}H_{20}NO_3$ $(M + H)^+$ 262.1443, found 262.1452. ^1H NMR (300 MHz, $CDCl_3$) *δ* 7.30−7.26 (m, 3H), 7.13−7.11 (m, 2H), 4.36 (apparent t, 1H, *J* = 4.6 Hz), 4.32 (d, 1H, *J* = 7.1 Hz), 3.31 (dd, 1H, *J* = 13.5, 4.6 Hz), 3.25 (dd, 1H, *J* = 13.5, 4.5 Hz), 2.95 (s, 3H), 1.23−1.11 (m, 1H), 0.83 (d, 3H, *J* = 6.8 Hz), 0.57 (d, 3H, *J* = 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 165.8, 164.5, 134.8, 129.8, 129.0, 127.7, 83.8, 61.9, 38.0, 32.8, 32.3, 18.8, 17.4.

Mitsunobu Cyclization of Compound 27: Fast Addition. Preparation of Bassiatin Enantiomer 7. To a premixed solution of **29** (170 mg, 0.65 mmol) and DEAD (100 μL, 0.65 mmol) in dry THF (22 mL) was added a solution of the peptide **27** (150 mg, 0.5 mmol) in dry THF (8 mL) over 10 min. During this period the reaction temperature was maintained at 0 °C, followed by stirring at room temperature for 18 h. The reaction mixture was then concentrated at reduced pressure. The solid residual products were first recrystallized with ethyl acetate−hexane, then further purified via flash chromatography eluting with 70:30:0.1 ether:hexane:Et_3N to give the depsipeptide **7** as a colorless solid (88 mg, 52%) that was identical with material described above.

Mitsunobu Cyclization of Compound 27: Slow Addition. Preparation of Depsipeptide 9. To a premixed solution of **29** (170 mg, 0.65 mmol) and DEAD (100 μL, 0.65 mmol) in dry THF (22 mL) was added a solution of the peptide **27** (150 mg, 0.5 mmol) in dry THF (8 mL) over 2 h. During this period the reaction temperature was maintained at 0 °C, followed by stirring at room temperature for 18 h. The reaction mixture was then concentrated at reduced pressure. The crude residue was purified by flash chromatography eluting with 80:20:0.1 ether:hexane:Et_3N to give the depsipeptide **9** as a colorless oil (70 mg, 54%). $[\alpha]^{21}_D$ +31.2 (*c* 1.0, CH_2Cl_2). FTIR (NaCl) *ν* 2968, 2939, 2879, 1744, 1666, 1499, 1455, 1404, 1377, 1342, 1282, 1252, 1200, 1137, 1043, 756, 702 cm^{-1}. HRMS (ES) *m/z* calcd for $C_{15}H_{20}NO_3$ $(M + H)^+$ 262.1443, found 262.1446. ^1H NMR (300 MHz, $CDCl_3$) *δ* 7.33−7.25 (m, 3H), 7.15−7.12 (m, 2H), 4.37 (apparent t, 1H, *J* = 4.5 Hz), 4.33 (d, 1H, *J* = 7.1 Hz), 3.33 (dd, 1H, *J* = 13.6, 4.6 Hz), 3.27 (dd, 1H, *J* = 13.5, 4.5 Hz), 2.96 (s, 3H), 1.22−1.15 (m, 1H), 0.83 (d, 3H, *J* = 6.8 Hz), 0.58 (d, 3H, *J* = 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 165.9, 164.6, 134.8, 129.8, 128.9, 127.8, 83.8, 61.9, 38.0, 32.9, 32.4, 18.8, 17.4.

Epimerisation Test of Depsipeptide 8. To a premixed solution of **29** (21 mg, 0.079 mmol) and DEAD (12 μL, 0.079 mmol) in dry THF (22 mL) was added a solution of the depsipeptide **8** (20 mg, 0.072 mmol) in dry THF (8 mL) over 10 min. During this period the reaction temperature was maintained at 0 °C, followed by stirring at room temperature for 18 h. The reaction mixture was then concentrated at reduced pressure. The crude residue was purified by flash chromatography eluting with 80:20:0.1 ether:hexane:Et_3N to give the depsipeptide **8**. The spectroscopic data of the product were identical with material prepared earlier.

Attempted Formation of the Anhydride 42. To a premixed solution of triphenylphosphine (33 mg, 0.13 mmol) and DEAD (20 μL, 0.13 mmol) in dry THF (2 mL) was added a solution of the amino acid **12a** (80 mg, 0.25 mmol) in dry THF (9 mL) over 10 min. During this period the reaction temperature was maintained at 0 °C, followed by stirring at room temperature for 18 h. The reaction mixture was monitored by TLC, which indicated that only the starting material was present.

Attempted Formation of the Anhydride 44. To a premixed solution of triphenylphosphine (41 mg, 0.16 mmol) and DEAD (24 μL, 0.16 mmol) in dry THF (2.4 mL) was added a solution of the amide **43** (105 mg, 0.33 mmol) in dry THF (10 mL) over 10 min. During this period the reaction temperature was maintained at 0 °C, followed by stirring at room temperature for 18 h. The reaction mixture was monitored by TLC, which indicated that only starting material was present.

Mitsunobu Cyclization of Compound 19: Preparation of Compound 10. This reaction was performed by the same method as described for the preparation of Bassiatin **1**.

Data for Compound 10. Colorless oil (50% yield). $[\alpha]^{26}_D$ +117.4 (*c* 0.87, CH_2Cl_2). Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.90; H, 7.40; N, 5.37. FTIR (NaCl) *ν* 3031, 2969, 2935, 1751, 1668, 1496, 1455, 1406, 1372, 1300, 1243, 1114, 1070, 923, 844, 813, 753, 701 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) *δ* 7.28−7.20 (m, 5H), 5.03 (dd, 1H, *J* = 6.9, 3.8 Hz), 3.64 (d, 1H, *J* = 6.2 Hz), 3.43 (dd, 1H, *J* = 14.5, 3.8 Hz), 3.17 (dd, 1H, *J* = 14.5, 7.0 Hz), 2.94 (s, 3H), 2.23−2.14 (m, 1H), 1.26 (d, 3H, *J* = 7.1 Hz), 1.08 (d, 3H, *J* = 6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 165.2, 165.1, 135.6, 130.0, 128.4, 127.2, 78.2, 67.4, 37.7, 34.4, 31.6, 19.5, 18.2.

Attempted Preparation of the Amide 20. The acid **5c** (379 mg, 1.8 mmol) and the amine **4c** (374 mg, 2.0 mmol) were dissolved in dry dichloromethane (2.2 mL). HATU (767 mg, 2.0 mmol) was added and the mixture was cooled to 0 °C. To the cooled mixture was added diisopropylethylamine (700 μL, 4.0 mmol). The reaction was left to stir at 0 °C for 2 h and then the reaction mixture was applied to a short silica column eluting with 20% ethyl acetate−hexane. The eluent was evaporated to dryness in vacuo and the crude residue was purified by flash chromatography on silica gel eluting with 20% ethyl acetate−hexane to give the amides **18** and **20** as a mixture (290 mg, 42%). A sample of this mixture was subjected to acidic hydrolysis as described for the preparation of the hydroxy acids **15**−**18** and **21**. The major product of the hydrolysis reaction following separation by column chromatography had a ^1H NMR spectrum identical in all respects with that of compound **19** described above. The minor hydrolysis component had the following ^1H NMR spectrum: ^1H NMR (300 MHz, $CDCl_3$) *δ* 7.29−7.24 (m, 5H), 5.03 (dd, 1H, *J* = 3.6, 8.1 Hz), 3.80 (d, 1H, *J* = 5.2 Hz), 3.38 (dd, 1H, *J* = 3.5, 14.4 Hz), 3.20 (dd, 1H, *J* = 8.2, 14.5 Hz), 2.99 (s, 3H), 2.03−1.92 (m, 1H), 1.07 (d, 3H, *J* = 6.9 Hz), 0.80 (d, 3H, *J* = 6.9 Hz).

Lactonization of Hydroxy Acid 19 To Give Depsipeptide 10. The amide **19** (50 mg, 0.18 mmol) was dissolved in dry dichloromethane (18 mL). DCC (45 mg, 0.22 mmol) was added to the solution and then it was cooled to 0 °C with an ice−water bath. DMAP (4 mg, 0.036 mmol) was added and the reaction mixture was stirred at 0 °C for 1 h. It was then left to stir at room temperature for 3 d. The urea precipitate was removed by filtration and the organic filtrate was diluted with ethyl acetate. The organic phase was then washed successively with saturated sodium bicarbonate solution, water, and dilute citric acid solution. The organic phase was dried ($MgSO_4$), filtered, and evaporated at reduced pressure. The residue was purified by column chromatography eluting with 40% ethyl acetate−hexane to afford the depsipeptide **10**, which had a ^1H NMR spectrum identical with that quoted above.

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